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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,190	GRIMPE ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,10-18,21-31 and 34-55* is/are pending in the application.

4a) Of the above claim(s) *4, 7, 10-11, 14-16, 21-22, 35, 37-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of claim amendments and applicant's remarks, filed 21 February 2008.

Claim Status

Claims 1, 4, 7, 10-17, 21-31, 34, 36-54 and 56 are pending. Claims 1, 17, and 29 are amended. Claims 2-3, 5-6, 8-9, 18-20, 32-34, 36, 55 are cancelled. Claim 56 is newly submitted. Claims 4, 7, 10-11, 14-16, 21-22, 35, 37-54 were withdrawn by the examiner in the previous Office Action, as being drawn to non-elected inventions. Claims 1, 12-13, 17, 23-25, 29 and 56 are under current examination.

Priority

This application claims benefit from provisional U.S. Application No. 60/423,082 filed 1 November 2002 and claims benefit from provisional U.S. Application No. 60/471,447 filed 16 May 2003. The instant application has been granted the benefit date, 1 November 2002 from the application 60/423,082.

Response to Arguments - Claim Objections

Applicant's arguments (Remarks, page 14) and Claim amendments, filed 21 February 2008, with respect to claim 18 have been fully considered and are persuasive. The objection to Claim 18 has been made moot by the claim amendments submitted on 21 February 2008 and are hereby withdrawn.

Response to Arguments - Claim Rejections 35 USC § 112

Response to Arguments – 35 USC 112, second paragraph

Applicant's arguments (Remarks, page 14) and Claim amendments, filed 21 February 2008, with respect to claim 30 have been fully considered and are persuasive. The rejections of claims 30 under 35 USC 112, second paragraph, has been made moot by the claim amendments submitted on 21 February 2008 and are hereby withdrawn.

Response to Arguments – Scope of Enablement (35 USC 112, 1st paragraph)

Applicant's arguments (Remarks, pages 14-15) and Claim amendments, filed 21 February 2008, with respect to claims 1-3, 12-13, 17-18, 23-31, 34, and 36 have been fully considered and are persuasive. The rejections of claims 1-3, 12-13, 17-18, 23-31, 34, and 36 under 35 USC 112, first paragraph (scope of enablement), have been made moot by the claim amendments submitted on 21 February 2008 and are hereby withdrawn.

Response to Arguments – Written Description (35 USC 112, 1st paragraph)

Applicant's arguments (Remarks, pages 15-16) and Claim amendments, filed 21 February 2008, with respect to claims 1-3, 12-13, 17-18, 23-31, 36, and 55 have been fully considered and are persuasive. The rejections of claims 1-3, 12-13, 17-18, 23-31, 36, and 55 under 35 USC 112, first paragraph (written description), have been made

moot by the claim amendments submitted on 21 February 2008 and are hereby withdrawn.

Response to Arguments - Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 29 remains rejected under 35 U.S.C. 103(a) as being obvious over Vale et al. (US2001/0049360, published Dec.6, 2001) for the reasons of record and the comments below. Claims 34 and 36 are withdrawn because of the applicant's claim amendments.

Claims 34 and 36 are cancelled; therefore the rejection is moot.

Applicant's arguments (Remarks, pages 16-18) and claim amendments filed 21 February 2008 have been fully considered but they are not persuasive.

The applicant argues that Vale et al. teaches a method of inhibiting inhibin/betaglycan complex formation rather than inhibition of expression of betaglycan by nucleic acids. Contrary to the applicant's assertion, Vale et al. teach, "the formation of inhibin/betaglycan complexes may be inhibited by reducing the expression of

betaglycan in the cells by either antisense inhibition or by mutagenesis of one or both betaglycan alleles" (page 2, paarg.0018).

Therefore, the examiner finds the applicant's arguments unpersuasive and hereby maintains the rejection of claim 29 remains rejected under 35 U.S.C. 103(a) as being obvious over Vale et al. for the reasons of record and the comments above.

The rejection of claims 29-31, 34 and 36 under 35 U.S.C. 103(a) as being obvious over Hodgson et al. (WO00/73509, IDS 2/14/2005) in view of Taylor et al. (DDT. 1999. vol.4, No.12: 562-567) is hereby withdrawn in response to the applicants arguments and claim amendments.

Applicant's arguments (Remarks, pages 18-19) and claim amendments filed 21 February 2008 have been fully considered and they are persuasive.

The applicant argues that the claims have been amended such that they no longer recite a limitation wherein the inhibition of GAG formation is by agents which inhibit chain sulfation. A major teaching of the prior art included in this 35 USC 103 rejection related to agents which inhibited heparin-sulfate 6-sulfotransferase. The art does not teach any of the remaining members of the Markush group. The examiner finds the applicant's argument persuasive.

Therefore, the examiner hereby withdraws the rejection of claims 29-31, 34 and 36 under 35 U.S.C. 103(a) as being obvious over Hodgson et al. in view of Taylor et al.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Margolis et al. (US-5,625,040).

Claim 29 is directed to a method for identifying and/or characterizing an agent, the method comprising screening a library of agents capable of one or more of the following: (i) inhibiting the expression of a primary proteoglycan; (ii) inhibiting the expression and/or activity of a chain initiation enzyme; (iii) inhibiting the expression and/or activity of a chain elongation enzyme; or (iv) promoting inter-mixing of Schwann cells and astrocytes. Claim 56 is directed to the method of claim 29, the primary proteoglycan being selected from the group consisting of neurocan, NG2, and phosphacan.

Margolis et al. teach nucleic acids encoding the phosphacan proteoglycans are useful in inhibiting or promoting neural cell adhesion and related activities important to neuronal development and regeneration (col.1, lines 14-21). Margolis et al. teach, "degenerate oligonucleotide primers based on the N-terminal amino acid sequence of the 3F8 [phosphacan] proteoglycans and the sequence of an internal CNBr peptide were synthesized….The PCR product was subcloned into pGEM3 and antisense RNA

transcripts were prepared for screening of the same cDNA library" (col. 15, lines 1-16). Margolis et al. teach using these digoxigenin-labeled riboprobes to detect expressed mRNA message for phosphacan in cells (col.20, Example V). Since the antisense riboprobes would be capable of inhibiting expression of phosphcan, the examiner believes the methods of Margolis et al. wherein antisense RNA transcripts were used in both the screening of the cDNA library and northern blots of Example V, satisfy the limitations of the instant claims.

Accordingly, Margolis et al. anticipated the instant claims, as broadly drawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 12-13, 17, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moyer (Neurology Today. October 2002; 2(1): 26, 28) in view of Kleesiek (WO01/49831) and further in view of Jen et al. (Stem Cells 2000; 18:307-319).

Claim 1 is directed to a method of reducing glycosaminoglycan (GAG) content in a glial scar of a mammal comprising administering to the glial scar of the mammal an agent that inhibits the expression and/or activity of a chain initiation enzyme wherein the agent is selected from the group consisting of antisense oligonucleotides, ribozymes, DNA enzymes, and RNAi constructs, the agent targeting a nucleic acid sequence encoding xylotransferase I (XT-I) or xylotransferase I I (XT-II); wherein the agent is administered intrathecally, topically, or locally to the glial scar.

Claim 17 is directed to a method of promoting neuronal regeneration in a subject comprising administering an agent to the to a nervous system lesion to inhibit a GAG chain initiation enzyme, wherein the agent is selected from the group consisting of antisense oligonucleotides, ribozymes, DNA enzymes, and RNAi constructs, the agent targeting a nucleic acid sequence encoding xylotransferase I (XT-I) or xylotransferase II (XT-II); wherein the agent is administered intrathecally, topically, or locally to the nervous system lesion; wherein the neuronal regeneration includes neurite extension into the nervous system lesion.

The remaining claims are directed to the agent being a DNA enzyme (claims 12 and 23) and wherein there is an additional administration of a growth factor or neurotrophic factor (claim 25). Claims 13 and 24 are directed to specific DNA enzymes SEQ ID NO:33 and 39.

Moyer teaches that the field of neurology has been "seeking to identify a way to target enzymes such as xylotransferase-1, which…[has the] potential for the regeneration of sensory neurons beyond the glial scar." (middle of page 3 from Welch Library FAX of Moyer)

Moyer et al. do not specifically suggest using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II.

Kleesiek teaches cloning of cDNA of human and rat xylotransferase-I and xylotransferase-II (XT-I and XT-II) and expression of recombinant proteins (abstract). Kleesiek teaches XT is the initial step enzyme in the biosynthesis of the glycosaminoglycan linkage region. (page 2, lines 8-9). Kleesiek teaches "knowledge of the cDNA sequence of XT allows to use it on gene level such as in gene diagnostic or gene therapy" (page 2, lines 25-26). Kleesiek suggests making medicaments which are inhibitors of xylosyltransferase (page 17, lines 3-4).

Kleesiek does not specifically teach using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II.

Jen et al. is a review article about designing antisense oligonucleotides, ribozymes, and DNAzymes. Jen et al. teaches "the DNAzyme can be made to cleave virtually any RNA that contains a purine-pyrimidine junction" (page 312, col.2). The

examiner believes that this teachings along with the teachings of Kleesiek which describe the DNA sequence for xylotransferase-I and xylotransferase-II, make any DNA enzyme obvious.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to reduce GAG content in a glial scar and promote neuronal regeneration in a subject by inhibiting XT-I or XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs.

The person of ordinary skill in the art would have been motivated to combine the teachings of Moyer et al., Kleesiek, and Jen et al. in a method using DNA enzymes (and other inhibitors of mRNA) to XT-I or XT-II to inhibit glial scar formation and promote neural regeneration. Moyer et al. suggest that the field of neurology had identified inhibiting xylotransferase as a method of "regeneration of sensory neurons beyond the glial scar." From

Absent evidence to the contrary, an artisan would have expected success, because use of antisense oligonucleotides are well known in the art to inhibit expression of genes by inhibiting mRNA. From the teachings of Kleesiek , it seems possible to use the "knowledge of the cDNA of XT-I and XT-II to make gene therapeutic inhibitors of XT-I and XT-II activity. Finally, Jen et al. suggest that any DNAzyme can be made, using knowledge of a given cDNA. Together, the prior art seems to provide all the known element required for using DNA enzymes for the inhibition of XT-I or XT-II.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior

art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (cDNA sequence of XT-I and XT-II; theory of DNAzyme design; importance of XT in glial scar formation and neuroregeneration) are taught by Moyer or Kleesiek or Jen. It would be therefore predictably obvious to use a combination of these three elements in a method using DNA enzymes (and other inhibitors of mRNA) to XT-I or XT-II to inhibit glial scar formation and promote neural regeneration. Furthermore, the specific DNA enzymes of SEQ ID NO:33 and 39 would be likewise obvious.

Therefore the method as taught by Moyer et al. in view of Kleesiek and further in view of Jen et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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